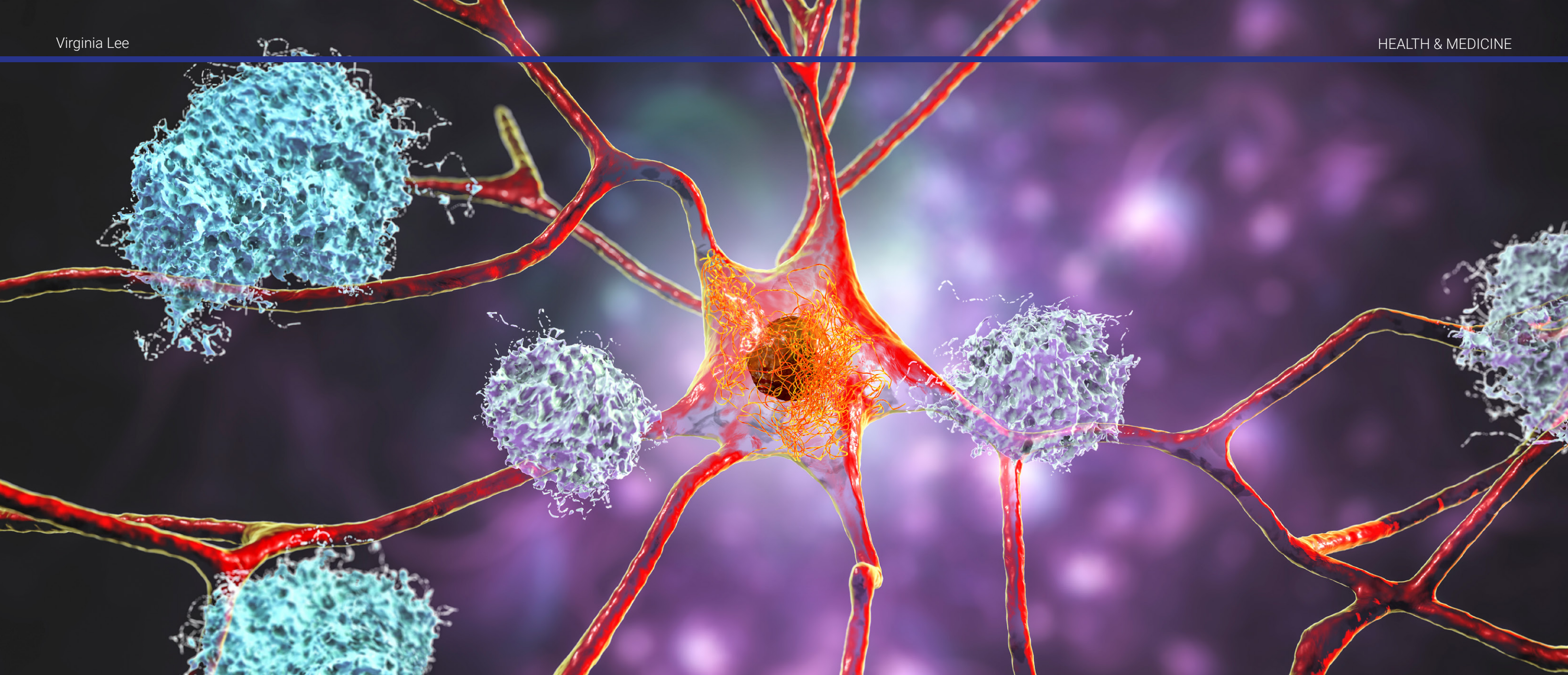




Cell-to-cell transmission of proteins is at the core of neurodegenerative disease

- One of the leading neuroscientists of a generation, Professor Virginia Lee at the University of Pennsylvania, USA, highlights the pivotal role of protein aggregates in the pathology of neurodegenerative diseases.
- Her landmark studies improve our understanding of the pathogenesis of misfolded proteins that clump together and propagate throughout the brain.
- These significant contributions are the epitome of translational research progressing drug discovery to try to help those affected.

Unfortunately, too many of us know someone affected by a neurodegenerative disease. Worldwide, this group of diseases marked by progressive loss of brain function has devastating consequences for patients and their families. Alzheimer's disease (AD), the most common of these late life neurodegenerative diseases, affects an estimated 24 million people worldwide, followed by Parkinson's disease (PD). Usually, these diseases present in older age; however, another neurodegenerative disease, frontotemporal degeneration (FTD), is typically diagnosed in middle age and indicative of early-onset dementia.

Professor Virginia Lee at the University of Pennsylvania, USA, has spent decades researching such neurodegenerative diseases to advance our understanding of the underlying pathological mechanisms in a nonstop quest for therapeutic development. With over 1,000 papers spanning an extensive career, Lee's contributions to this field are both significant and vast. Here, we take a closer look at her

studies around the novel discovery of cell-to-cell transmission of misfolded proteins in the progression of neurodegenerative diseases.

Understanding proteinopathies

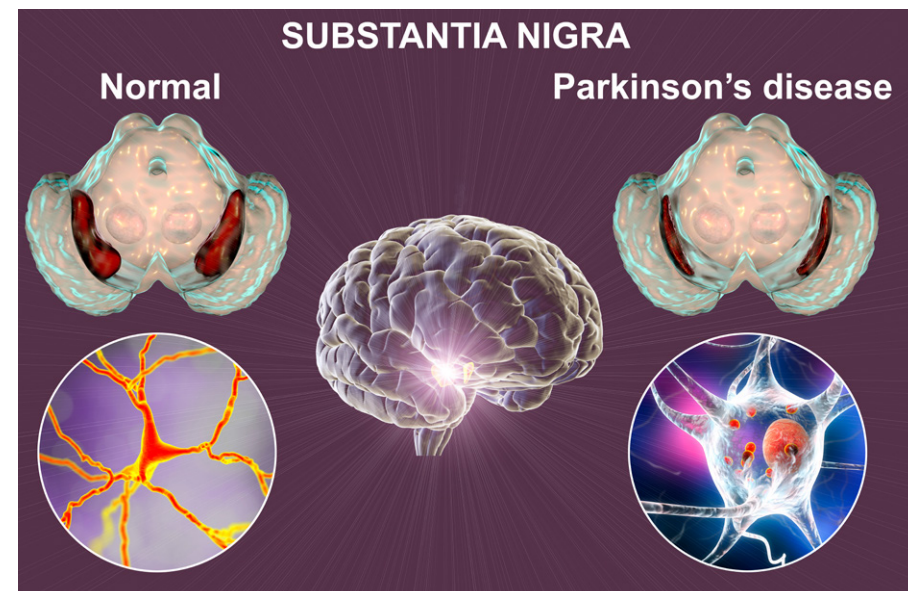
A hallmark of several neurodegenerative diseases such as AD, PD, frontotemporal lobar degeneration (FTLD-TDP), and amyotrophic lateral sclerosis (ALS) is the presence of misfolded protein deposits in the brain, giving them the collective term 'proteinopathies'. But what causes these proteins to aggregate and how do they propagate through the brain? Pioneering studies by Lee and colleagues in 2014 and 2015 furthered our understanding of this. They suggest proteins become misfolded and, when released, corrupt other cells, causing them to also produce misfolded proteins. Over time this abnormal protein

structure propagates from cell to cell and throughout the brain, depicting the widespread protein deposits seen in disease.

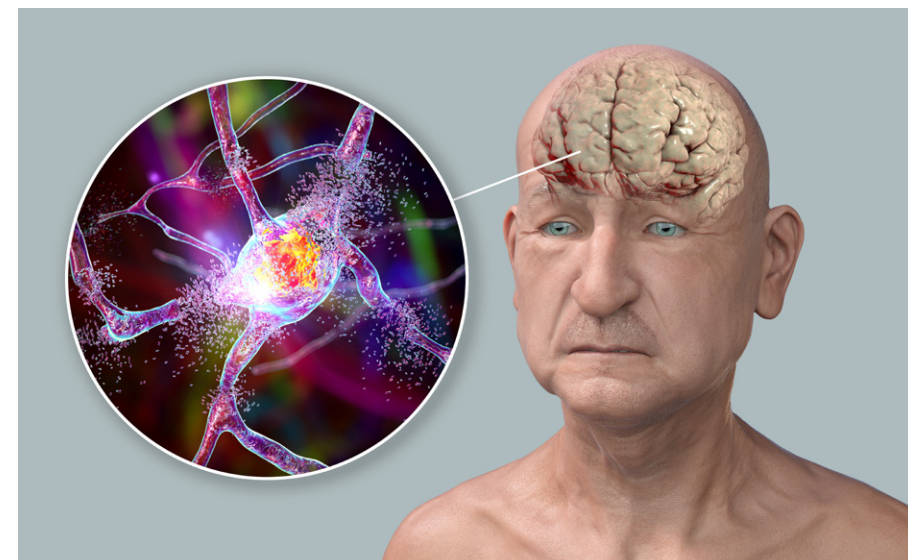
If we can understand diseases, what causes them and how they progress, we can develop treatments for them. Developing novel and relevant animal models that enable the study of disease pathogenesis found in humans has been a fundamental part of Lee and her team's research. Their work has focused on deriving proteins from postmortem human brain for use in models to better study proteinopathies.

Brain deposits of misfolded TAR DNA-binding protein 43 (TDP-43) are characteristic of FTLD-TDP and ALS. In her 2018 paper, Lee demonstrated the cell-to-cell transmission of TDP-43 in mice for the first time. In fact,

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Normal substantia nigra (part of the basal ganglia in the brain; left) and substantia nigra affected by Parkinson's disease (right). The latter shows an accumulation of Lewy bodies in neurons.



Alzheimer's disease leads to progressive impairment of brain functions (neurodegeneration) in elderly age.

this groundbreaking study showed that injecting human-derived abnormal TDP-43 into mice brain induces TDP-43 pathology, which spreads over time. Ageing and cellular stress – conditions known to affect homeostasis – may lead to the accumulation of cellular TDP-43. Such cellular accumulation may act as 'seeds' leading to the growth and spread of TDP-43 in the brain, with certain neuronal types more susceptible to form aggregates than others.

The role of tau in Alzheimer's disease

Another protein, well known for its role in AD, is tau. Neurofibrillary tangles or 'threads' of tau protein accumulate in the cytoplasm of

neurons and together with β -amyloid ($A\beta$) are key features central to AD pathogenesis. Models used to study tauopathies have been questioned for their applicability in humans because they are simulated by conditions of tau overexpression and mutations, both of which are rarely found in human patients.

To address the challenges with current models, Lee and team used pathological tau enriched from AD brains instead of aggregated recombinant tau to induce tau pathology in mice. This method was better for 'seeding' or inducing tau aggregates in multiple brain regions. More than that, it demonstrated the importance of tau cell-to-cell transmission and indicated where in the

brain this occurred. Only certain brain regions were affected, suggesting these areas may be more susceptible to tau transmission or that transmission to the unaffected areas is prevented by some mechanism. Either way, this doesn't mimic or explain the widespread tau aggregation seen in humans with AD. The researchers think co-existing pathology such as β -amyloid ($A\beta$) may amplify the misfolded tau that spreads so widely in human brains. Not only has this study provided novel insights and confirmed that cell-to-cell transmission is a pivotal factor in tau pathology, but importantly, it provides a more physiologically relevant model for studying tau pathological mechanisms and investigating therapeutics to treat tauopathies.

Lewy bodies and α -Syn pathology

Misfolded alpha-synuclein (α -Syn) aggregates during pathological conditions, forming inclusions known as Lewy bodies (LBs). Although predominantly made up of α -Syn, LBs also contain other proteins and cellular materials. These insoluble clumps are a key feature of PD and other neurodegenerative diseases. In laboratory conditions, the small building blocks (monomers) of α -Syn aggregate to form amyloid fibrils known as pre-formed fibrils (PFFs). These PFFs are routinely used experimentally in mouse brains to study the pathology and spread of α -Syn associated neurodegenerative conditions.

In a major step forward in the study of Lewy body-associated neurodegenerative diseases, Lee showed for the first time ever that pathological α -Syn isolated from postmortem AD and PD brains can not only be able experimentally to induce α -Syn pathology in mouse neurons, but that this pathology differs from those induced by PFFs. Differences in regional distribution of α -Syn inclusions as well as their shape, size and quantity were evident. Considering the limited availability of human brain-derived α -Syn, the team experimentally amplified brain derived pathological α -Syn with recombinant α -Syn, and by doing so, ensured adequate supplies of pathological α -Syn for use in future research. This study does not dispute the utility of α -Syn PFFs for studying α -Syn pathology but highlights potential limitations of the model when exploring the pathology of human disease. The researchers expect the new model will enable extensive investigations of α -Syn pathology in the pursuit of new therapies.

With such a high disease burden and mortality, research on neurodegenerative conditions must continue to advance. The recent improvements in relevant animal models are likely to be key. With Lee and team at the forefront of such research, the hope is that we will gain a deeper understanding of proteinopathies and how best to treat them.

Personal response

What led you to study neurodegenerative diseases?

I was trained as a protein biochemist. For my PhD, I learned about protein fractionation and purification from tissues and cells, and for my postdoctoral fellowship I learned neuroscience and animal models. Beginning in the 1990s, my late husband John and I decided to collaborate very closely to identify all misfolded proteins involved in neurodegenerative diseases since we were in a unique position to undertake this important project, with John being the neuropathologist and me being a protein biochemist. Indeed, it resulted in many fruitful and important collaborations.

What advice would you give a young researcher who's interested in getting started in your field?

Young researchers need to develop an in-depth understanding of the clinical

presentation and neuropathology of the neurodegenerative diseases they are working on. Without this knowledge, they would not be able to interpret and understand the implication of their findings.

Are there any things that have surprised you during your studies on cell-to-cell transmission of proteins in neurodegenerative diseases?

Yes – that misfolded proteins such as tau and TDP-43 with diverse functions and biochemical properties all undergo similar cell-to-cell transmission.

What could your work one day mean for patients suffering with neurodegenerative diseases?

I hope that our work can one day lead to the identification of more tractable targets for the development of effective therapy to delay the onset or provide treatment for these devastating diseases.

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Further reading

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